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Power and Related Statistical Properties of Conditional Likelihood Score Tests for Association Studies in Nuclear Families with Parental Genotypes

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Summary

Both population based and family based case control studies are used to test whether particular genotypes are associated with disease. While population based studies have more power, cryptic population stratification can produce false-positive results. Family-based methods have been introduced to control for this problem. This paper presents the full likelihood function for family-based association studies for nuclear families ascertained on the basis of their number of affected and unaffected children. The likelihood of a family factors into the probability of parental mating type, conditional on offspring phenotypes, times the probability of offspring genotypes given their phenotypes and the parental mating type. The first factor can be influenced by population stratification, whereas the latter factor, called the conditional likelihood, is not. The conditional likelihood is used to obtain score tests with proper size in the presence of population stratification (see also Clayton (1999) and Whittemore & Tu (2000)). Under either the additive or multiplicative model, the TDT is known to be the optimal score test when the family has only one affected child. Thus, the class of score tests explored can be considered as a general family of TDT-like procedures. The relative informativeness of the various mating types is assessed using the Fisher information, which depends on the number of affected and unaffected offspring and the penetrances. When the additive model is true, families with parental mating type $Aa \times Aa$ are most informative. Under the dominant (recessive) model, however, a family with mating type $Aa \times aa$ ($AA \times Aa$) is more informative than a family with doubly heterozygous ($Aa \times Aa$) parents. Because we derive explicit formulae for all components of the likelihood, we are able to present tables giving required sample sizes for dominant, additive and recessive inheritance models.

Introduction

To test whether particular genes are associated with disease, epidemiologists and geneticists use both population-based and family-based case-control designs. Both designs compare frequencies of particular alleles or genotypes of cases to those of controls. Population-based case-control designs with unrelated controls have greater power for detecting an association, and are easier to implement compared with family-based case-control designs (Risch & Teng, 1998; Teng & Risch, 1999; Witte *et al.* 1999). However, the population-based case-control design is subject to spurious association arising from population stratification (Li, 1969; Lander & Schork, 1994; Ewens & Spielman, 1995). Family-based case-control designs are more robust to potential confounding from population stratification because they match the genetic background of the case and control groups. Although some family-based association tests do not require parental genotype information (Boehnke & Langefeld, 1998; Horvath & Laird, 1998; Zhao *et al.*

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1997), many procedures are based on nuclear families with genetic marker information from parents and an affected offspring (Falk & Rubinstein, 1987; Ott, 1989; Self *et al.* 1991; Terwilliger & Ott, 1992; Spielman *et al.* 1993; Schaid & Summer, 1993; Thomson, 1995; Schaid, 1996; Kaplan & Martin, 2001). A prime example of a family-based association test is the transmission/disequilibrium test (TDT) (Spielman *et al.* 1993). The TDT test relies on data on transmission of marker alleles from heterozygous parents to affected offspring. Ewens & Spielman (1995) showed that the TDT is robust to admixture and population stratification. Curnow *et al.* (1998) and Schaid (1998) have examined many extensions of the TDT and their properties.

Whittemore & Halpern (2003) reviewed and compared three types of procedures for detecting genetic associations with disease from nuclear families with affected and unaffected offspring, and from more general pedigrees. One class of procedures is based on the conditional distribution of offspring genotypes given offspring disease status and parental genotypes (Self *et al.* 1991; Schaid & Sommer, 1993; Schaid, 1996; Clayton & Jones, 1999; Clayton, 1999; Whittemore & Tu, 2000; Tu *et al.* 2000; Shih & Whittemore, 2002), sometimes termed as "non-founder statistics" (Whittemore & Tu, 2000) or "conditional on parental genotypes" statistics (Schaid & Sommer, 1993). Clayton (1999), Whittemore & Tu (2000) and Shih & Whittemore (2002) described a modification that can be used when some parental genotype information is missing. Rabinowitz & Laird (2000) proposed conditioning on sufficient statistics for the missing parental genotypes, to develop so called FBAT tests, while Rabinowitz (2003) proposed a less restrictive conditioning. All of these procedures yield equivalent tests with complete parental genotype information, the case we are considering, as does the score procedure of Schaid & Sommer (1993). Our principal contribution is to give explicit formulae for all components of the likelihood, which enables us to derive explicit sample size formulae. In the discussion, we compare our results with earlier work on power for FBAT (Lange & Laird, 2002a,b) and for TDT type tests (Chen & Deng, 2001), the latter based on Knapp (1999).

In particular, we derive the likelihood function for nuclear families with both affected and unaffected offspring. It factors into three parts: 1) the conditional parental genotype probabilities given affection status of offspring; 2) the conditional genotype distribution of affected offspring given the parental mating type and affection status of offspring; and 3) the conditional genotype distribution of unaffected offspring given the parental mating type and affection status of offspring. We call the product of the latter two factors the conditional likelihood. As in Schaid (1996), Clayton (1999) and Whittemore & Tu (2000), we develop score tests from the conditional likelihood which are robust against population stratification. The class of conditional likelihood score tests (CLST) contains the TDT, which is the CLST under additive or multiplicative models. The TDT is not equivalent to conditional likelihood score tests derived under a dominant or recessive genetic model, however. Because we have explicit formulae for the first component of likelihood above, we can calculate the power of these score tests; we present tables of required sample sizes for the CLSTs for additive, dominant and recessive penetrance models.

Methods

Likelihoods

We consider a biallelic candidate disease locus with alleles A and a. Nuclear families with r_i affected and s_i unaffected sibs and their parents are ascertained for an association study. Let $t_i = r_i + s_i$ be the sibship size for the ith family. For notational simplicity, the index i will be omitted when we discuss the likelihood function, score function or observed information matrix for a family. The three penetrances are denoted by

$$f_2 = P\{\text{Aff}|AA\}, \quad f_1 = P\{\text{Aff}|Aa\},$$

$$f_0 = P\{\text{Aff}|aa\},$$

where "Aff" denotes affected and "Unaff" unaffected disease status. The null hypothesis we are interested in testing is: $H_0 : f_2 = f_1 = f_0$, where the baseline penetrance f_0 is a known constant.

The nine possible joint parental genotypes are represented by $G = (i, j)$, where $i(j)$ is the number of A alleles carried by the first (second) parent. For example, $G = (1, 1)$ represents the parental mating type in which both parents are heterozygous with

Table 1 Conditional Parental Genotype Probabilities for Families with r Affected and s Unaffected Sibs

$G=(i,j)$	Conditional Probability $m_{ij}^{(r,s)}$
(2,2)	$\frac{\binom{r+s}{r}}{K_{r,s}} f_2^r (1-f_2)^s g_{22}$
(2,1)	$\frac{\binom{r+s}{r}}{K_{r,s}} (\frac{1}{2})^t (f_2+f_1)^r [(1-f_2)+(1-f_1)]^s g_{21}$
(1,2)	$\frac{\binom{r+s}{r}}{K_{r,s}} (\frac{1}{2})^t (f_2+f_1)^r [(1-f_2)+(1-f_1)]^s g_{12}$
(2,0)	$\frac{\binom{r+s}{r}}{K_{r,s}} f_1^r (1-f_1)^s g_{20}$
(0,2)	$\frac{\binom{r+s}{r}}{K_{r,s}} f_1^r (1-f_1)^s g_{02}$
(1,1)	$\frac{\binom{r+s}{r}}{K_{r,s}} (\frac{1}{4})^t (f_2+2f_1+f_0)^r \times [(1-f_2)+2(1-f_1)+(1-f_0)]^s g_{11}$
(1, 0)	$\frac{\binom{r+s}{r}}{K_{r,s}} (\frac{1}{2})^t (f_1+f_0)^r [(1-f_1)+(1-f_0)]^s g_{10}$
(0,1)	$\frac{\binom{r+s}{r}}{K_{r,s}} (\frac{1}{2})^t (f_1+f_0)^r [(1-f_1)+(1-f_0)]^s g_{01}$
(0,0)	$\frac{\binom{r+s}{r}}{K_{r,s}} f_0^r (1-f_0)^s g_{00}$

genotype Aa. The population frequency of the joint genotype $G=(i,j)$ is denoted by $g_{ij}=P\{G=(i,j)\}$. The conditional parental mating type probability is $m_{ij}^{(r,s)}=P\{G=(i,j)|C_r=\text{Aff}, C_s=\text{Unaff}\}$, where the event that r sibs are affected is denoted by $C_r=\text{Aff}$, and the event that s sibs are unaffected is denoted by $C_s=\text{Unaff}$. Under the null hypothesis, the conditional mating type probability $m_{ij}^{(r,s)}$ is the unconditional mating type probability g_{ij}. Formulae for $m_{ij}^{(r,s)}$ are given in Table 1, where $K_{r,s}=P\{C_r=\text{Aff}, C_s=\text{Unaff}\}$. Derivations of the formulae in Table 1 are given in Li *et al.* (2001) and are based on the assumption that disease risks among family members are conditionally independent given their genotypes. Note that the g_{ij} need not conform to random mating under Hardy-Weinberg equilibrium in this analysis.

For any given family, the genotype status of the offspring can be represented as a random vector $(j_2, j_1, j_0, k_2, k_1, k_0)$, where $j_i(k_i)$, $i=0,1,2$, is the number of affected (unaffected) sibs with i A alleles. We have $j_2+j_1+j_0=r$, and $k_2+k_1+k_0=s$. The likelihood function for any given family is

$$P\{j_2, j_1, j_0, k_2, k_1, k_0, G|C_r=\text{Aff}, C_s=\text{Unaff}\} = m_G^{(r,s)} h_G^A(j_2, j_1, j_0) h_G^U(k_2, k_1, k_0), \quad (1)$$

where $m_G^{(r,s)}=m_{ij}^{(r,s)}$ with $G=(i,j)$ and where

$$h_G^A(j_2, j_1, j_0) = \binom{r}{j_2, j_1, j_0} \left(\frac{\tau_{G2} f_2}{\sum_{l=0}^2 \tau_{Gl} f_l}\right)^{j_2} \times \left(\frac{\tau_{G1} f_1}{\sum_{l=0}^2 \tau_{Gl} f_l}\right)^{j_1} \left(\frac{\tau_{G0} f_0}{\sum_{l=0}^2 \tau_{Gl} f_l}\right)^{j_0} \quad (2)$$

is the conditional genotype distribution of affected offspring given both the parental mating type and affection status of offspring. Similarly,

$$h_G^U(k_2, k_1, k_0) = \binom{s}{k_2, k_1, k_0} \left(\frac{\tau_{G2}(1-f_2)}{\sum_{l=0}^2 \tau_{Gl}(1-f_l)}\right)^{k_2} \times \left(\frac{\tau_{G1}(1-f_1)}{\sum_{l=0}^2 \tau_{Gl}(1-f_l)}\right)^{k_1} \times \left(\frac{\tau_{G0}(1-f_0)}{\sum_{l=0}^2 \tau_{Gl}(1-f_l)}\right)^{k_0} \quad (3)$$

is the conditional genotype distribution of unaffected offspring given both the parental genotype and affection status of the offspring. Sometimes h_G^A and h_G^U are used in place of $h_G^A(j_2, j_1, j_0)$ and $h_G^U(k_2, k_1, k_0)$, respectively. Finally, $\tau_{G2}=P\{\text{C}=\text{AA}|G\}$ is the conditional probability that a child has genotype AA given the parental genotype is G. Similarly, $\tau_{G1}=P\{\text{C}=\text{Aa}|G\}$ and $\tau_{G0}=P\{\text{C}=\text{aa}|G\}$. The derivation of the likelihood (1) is given in Appendix A. Notice that $h_G^A(j_2, j_1, j_0)$ and $h_G^U(k_2, k_1, k_0)$ do not depend on the population mating frequencies (g_{ij}) or allele frequency (p). Thus, population stratification has no effect on the conditional likelihoods ((2) and (3)). The conditional mating type probabilities, $m_G^{(r,s)}$, however, depend on the population mating frequencies, g_{ij}. Hence, they may be affected by population stratification. Even if there is random mating within each of several subpopulations, the g_{ij} will differ among the subpopulations if the allele frequencies vary among them.

Conditional Likelihood Score Tests for Additive, Dominant and Recessive Penetrance Models

We use the conditional likelihoods (2) and (3) to derive the score tests for additive, dominant and recessive penetrance models. The conditional likelihoods (2)

and (3) are binomial or trinomial distributions for a given parental mating type and a specific genetic model. For example, given the parental genotype $G = (1, 1) = Aa \times Aa$, the likelihood (2) has the trinomial distribution:

$$h_G^A = \binom{r}{j_2, j_1, j_0}\left(\frac{f_2}{f_2 + 2f_1 + f_0}\right)^{j_2} \times \left(\frac{2f_1}{f_2 + 2f_1 + f_0}\right)^{j_1}\left(\frac{f_0}{f_2 + 2f_1 + f_0}\right)^{j_0}.$$

If the mode of inheritance is additive, i.e., $f_1 = \frac{f_2+f_0}{2}$, then h_G^A becomes

$$h_G^A = \binom{r}{j_2, j_1, j_0}\left(\frac{f_2}{2(f_2 + f_0)}\right)^{j_2}\left(\frac{1}{2}\right)^{j_1} \times \left(\frac{f_0}{2(f_2 + f_0)}\right)^{j_0}.$$

The likelihood (3), h_G^U, has the same structure as h_G^A.

Additive Model

Under the additive penetrance model, $f_1 = \frac{f_2+f_0}{2}$, the null hypothesis H_0 is: $f_2 = f_0$ while the alternative hypothesis is $H_a : f_2 > f_0$. To derive the conditional score test for the additive genetic model, one first differentiates the log conditional likelihood function, $\log h_G^A h_G^U$, with respect to f_2 to obtain the score function and then evaluates the score function at the null hypothesis $f_2 = f_0$ to yield a conditional score for each family. Since families are independent, summing the conditional scores gives the total conditional score, U_{Add} in (4). To standardize U_{Add}, an estimator of the null variance of U_{Add} is needed. Often, the observed information is used as an estimator of the variance of U_{Add} under H_0. The observed information is minus the second derivative of the sum of the log conditional likelihoods (2) and (3) evaluated at $H_0 : f_2 = f_0$. This leads to the total observed information, V_{Add} in (4). The total score and the observed information are given by

$$U_{Add} = \frac{1}{f_0(1 - f_0)}\sum_{i=1}^{N} \times \left\{(1 - f_0)\left[j_{2i} - r_i\tau_{G2} + \frac{1}{2}(j_{1i} - r_i\tau_{G1})\right] - f_0\left[k_{2i} - s_i\tau_{G2} + \frac{1}{2}(k_{1i} - s_i\tau_{G1})\right]\right\},$$

$$V_{Add} = \frac{1}{f_0^2(1 - f_0)^2}\sum_{i=1}^{N} \times \left\{(1 - f_0)^2\left[j_{2i} + \frac{1}{4}j_{1i} - r_i\left(\tau_{G2} + \frac{1}{2}\tau_{G1}\right)^2\right] + f_0^2\left[k_{2i} + \frac{1}{4}k_{1i} - s_i\left(\tau_{G2} + \frac{1}{2}\tau_{G1}\right)^2\right]\right\}. \quad (4)$$

The probabilities τ_{G2} and τ_{G1} in (4) depend on the parental genotypes, which vary from family to family. To simplify notation the index i is not used. Although the statistic $T_{Add} = \frac{U_{Add}}{\sqrt{V_{Add}}}$ converges in distribution to a standard normal distribution under H_0, simulations indicate that U_{Add} and V_{Add} are highly correlated and thus T_{Add} has a size and power that differ from those predicted by asymptotic theory unless samples are very large. Therefore the following variance estimate is recommended. Note that $E_{H_0}(j_{2i}|G) = r_i\tau_{G2}$, $E_{H_0}(k_{2i}|G) = s_i\tau_{G2}$, $E_{H_0}(j_{1i}|G) = r_i\tau_{G1}$, and $E_{H_0}(k_{1i}|G) = s_i\tau_{G1}$. We propose replacing j_{2i}, k_{2i}, j_{1i}, and k_{1i} by $r_i\tau_{G2}$, $s_i\tau_{G2}$, $r_i\tau_{G1}$, and $s_i\tau_{G1}$, respectively. The modified score test statistic is

$$T^*_{Add} = \frac{U_{Add}}{\sqrt{V^*_{Add}}}, \quad (5)$$

where

$$V^*_{Add} = \frac{1}{f_0^2(1 - f_0)^2}\sum_{i=1}^{N} \times \left\{(1 - f_0)^2 r_i\left[\tau_{G2} + \frac{1}{4}\tau_{G1} - \left(\tau_{G2} + \frac{1}{2}\tau_{G1}\right)^2\right] + f_0^2 s_i\left[\tau_{G2} + \frac{1}{4}\tau_{G1} - \left(\tau_{G2} + \frac{1}{2}\tau_{G1}\right)^2\right]\right\}.$$

Unreported simulations indicate that normal theory predicts the size and power of tests based on T^*_{Add} very well.

To compute the power of T^*_{Add}, we assume that $r_i = r$ and $s_i = s$ for $i = 1, \ldots, N$. Under H_0, we have

$$E_{H_0}(U_{Add}) = 0, \quad Var_{H_0}(U_{Add}) = N\sigma^2_{0Add},$$

where

$$\sigma^2_{0Add} = \frac{1}{16}\left[\frac{r}{f_0^2} + \frac{s}{(1 - f_0)^2}\right][g_{(21)} + 2g_{11} + g_{(10)}]. \quad (6)$$

Here, $g_{(ij)} = g_{ij} + g_{ji}$ when $i \neq j$. Under H_a, the expectation and the variance of the score are

$$E_{H_a}(U_{Add}) = N\mu_{a\,Add}, \quad Var_{H_a}(U_{Add}) = N\sigma^2_{a\,Add}.$$

The formulae and derivations for μ_{aAdd} and σ^2_{aAdd} are given in Appendix B.

By the law of large numbers, the observed information divided by N, V^*_{Add}/N, converges to σ^2_{0Add} in probability under H_0. Under H_a, it converges to σ^2_{*Add} in probability, where

$$\sigma^2_{*Add} = \frac{1}{16}\left[\frac{r}{f_0^2} + \frac{s}{(1-f_0)^2}\right]\left[m^{(r,s)}_{(21)} + 2m^{(r,s)}_{11} + m^{(r,s)}_{(10)}\right].$$

When $i \neq j$, $m^{(r,s)}_{(ij)} = m^{(r,s)}_{ij} + m^{(r,s)}_{ji}$. Notice that σ^2_{*Add} equals neither σ^2_{0Add} nor σ^2_{aAdd}. If the one-sided score test T^*_{Add} is used, the sample size formula for level α and power $1-\beta$ is

$$N_{Add} = \frac{(\sigma_{*Add}z_{1-\alpha} + \sigma_{aAdd}z_{1-\beta})^2}{\mu^2_{aAdd}}, \tag{7}$$

where $z_{1-\alpha}$ and $z_{1-\beta}$ are percentiles of the standard normal distribution. Under H_a, we $f_2 = \gamma^2 f_0$ for $\gamma^2 > 1$. With f_0 and f_2 specified, all the terms in (7) can be computed. Kaplan & Martin (2001) studied the power of tests based on counts of alleles in affected versus unaffected offspring, whereas our statistics are based on individual genotypes. Under H_0, the two types of statistics have different variances (see Sasieni, 1997). Nevertheless, our score for the additive model counts alleles and resembles the methods in Kaplan & Martin (2001), but our statistics for dominant and recessive models do not count alleles.

Dominant Model

Under the dominant model, $f_1 = f_2$ and H_0 is: $f_2 = f_0$, while H_a is : $f_2 > f_0$. The score (U) and the observed information (V) for a sample of N families are

$$\begin{aligned} U_{Dom} &= \frac{1}{f_0(1-f_0)}\sum_{i=1}^{N}\{(1-f_0)[j_{2i} + j_{1i} - r_i(\tau_{G2} \\ &\quad + \tau_{G1})] - f_0[k_{2i} + k_{1i} - s_i(\tau_{G2} + \tau_{G1})]\}, \\ V_{Dom} &= \frac{1}{f_0^2(1-f_0)^2}\sum_{i=1}^{N}\{(1-f_0)^2[j_{2i} + j_{1i} - r_i(\tau_{G2} \\ &\quad + \tau_{G1})^2] + f_0^2[k_{2i} + k_{1i} - s_i(\tau_{G2} + \tau_{G1})^2]\}. \end{aligned} \tag{8}$$

As for the additive model, we recommend the modified score statistic

$$T^*_{Dom} = \frac{U_{Dom}}{\sqrt{V^*_{Dom}}}, \tag{9}$$

where

$$\begin{aligned} V^*_{Dom} &= \frac{1}{f_0^2(1-f_0)^2}\sum_{i=1}^{N} \\ &\quad \times \{(1-f_0)^2 r_i[\tau_{G2} + \tau_{G1} - (\tau_{G2} + \tau_{G1})^2] \\ &\quad + f_0^2 s_i[\tau_{G2} + \tau_{G1} - (\tau_{G2} + \tau_{G1})^2]\}. \end{aligned} \tag{10}$$

We compute the power and the required sample sizes for the test $T^*_{Dom} > z_{1-\alpha}$ under the assumption $r_i = r$ and $s_i = s$ for $i = 1, \ldots, N$. The expectations and variances of the score U_{Dom} under the alternative hypotheses can be expressed as $E_{H_a}(U_{Dom}) = N\mu_{aDom}$, and $Var_{H_a}(U_{Dom}) = N\sigma^2_{aDom}$, which are given in Appendix C. Setting $f_2 = f_0$ in μ_{aDom} and σ^2_{aDom}, yields the corresponding moments under H_0:

$$E_{H_0}(U_{Dom}) = N\mu_{0Dom} = 0,$$

$$\begin{aligned} \sigma^2_{0Dom} &= \frac{1}{N}Var_{H_0}(U_{Dom}) \\ &= \frac{1}{16}\left[\frac{r}{f_0^2} + \frac{s}{(1-f_0)^2}\right][3g_{11} + 4g_{(10)}]. \end{aligned}$$

Again, V^*_{Dom}/N converges in probability to σ^2_{0Dom} under H_0 and to $\sigma^2_{*Dom} = \frac{1}{16}[\frac{r}{f_0^2} + \frac{s}{(1-f_0)^2}][3m^{(r,s)}_{11} + 4m^{(r,s)}_{(10)}]$ under H_a. The sample size formula for a one-sided test based on T^*_{Dom} is given by (7) with the parameters μ_{aDom}, σ_{aDom}, and σ_{*Dom} in place of μ_{Add}, σ_{aAdd} and σ_{*Add}.

Recessive Model

For the recessive model $f_1 = f_0$, so the null hypothesis is $f_2 = f_0$ and the alternative hypothesis is $H_a : f_2 > f_0$. The score and the observed information are

$$\begin{aligned} U_{Rec} &= \frac{1}{f_0(1-f_0)}\sum_{i=1}^{N}\{(1-f_0)(j_{2i} - r_i\tau_{G2}) \\ &\quad - f_0(k_{2i} - s_i\tau_{G2})\}, \\ V_{Rec} &= \frac{1}{f_0^2(1-f_0)^2}\sum_{i=1}^{N}\{(1-f_0)^2(j_{2i} - r_i\tau^2_{G2}) \\ &\quad + f_0^2(k_{2i} - s_i\tau^2_{G2})\}. \end{aligned} \tag{11}$$

The modified score test statistic is

$$T^*_{Rec} = \frac{U_{Rec}}{\sqrt{V^*_{Rec}}}, \tag{12}$$

where

$$V^*_{Rec} = \frac{1}{f_0^2(1-f_0)^2}\sum_{i=1}^{N}\{(1-f_0)^2 r_i(\tau_{G2}-\tau_{G2}^2) + f_0^2 s_i(\tau_{G2}-\tau_{G2}^2)\}. \quad (13)$$

Assuming that $r_i = r$ and $s_i = s$ for $i = 1, \ldots, N$. The expectation and variance of the score U_{Rec} under the alternative hypotheses can be written as:

$$E_{H_a}(U_{Rec}) = N\mu_{a\,Rec}, \quad Var_{H_a}(U_{Rec}) = N\sigma^2_{a\,Rec}.$$

The formulae for μ_{aRec} and σ_{aRec} are presented in Appendix D. Setting $f_2 = f_0$ in these formulae yields the corresponding moments under H_0, i.e.,

$$E_{H_0}(U_{Rec}) = N\mu_{0\,Rec} = 0,$$

$$Var_{H_0}(U_{Rec}) = N\sigma^2_{0Rec} = N\frac{1}{16}\left[\frac{r}{f_0^2}+\frac{s}{(1-f_0)^2}\right] \times [4g_{(21)}+3g_{11}].$$

The quantity V^*_{Rec}/N converges in probability to σ^2_{0Rec} under H_0 and to σ^2_{*Rec} under H_a, where

$$\sigma^2_{*Rec} = \frac{1}{16}\left[\frac{r}{f_0^2}+\frac{s}{(1-f_0)^2}\right]\left[4m^{(r,s)}_{(21)}+3m^{(r,s)}_{11}\right].$$

The sample size formula for a one-sided test based on T^*_{Rec} is given by (7) with μ_{aRec}, σ_{aRec} and σ_{*Rec} in place of μ_{aAdd}, σ_{aAdd} and σ_{*Add}.

The quantities T^*_{Add}, T^*_{Dom} and T^*_{Rec} involve the background penetrance parameter f_0 except in the special cases of no unaffected offspring ($s = 0$) or no affected offspring ($r = 0$). We suggest using background disease risks and assumptions on the inheritance model to approximate f_0 (see Discussion). Even if f_0 is misspecified, tests based on T^*_{Add}, T^*_{Dom} and T^*_{Rec} have proper size. As we describe in the Discussion, estimates of required sample size and power calculations are somewhat sensitive to misspecification of f_0, although, for a given data set, misspecification of f_0 has relatively little impact on the test statistics T^*_{Add}, T^*_{Dom} and T^*_{Rec}.

Results

TDT as a Conditional Likelihood Score Test under Additive or Multiplicative Models

The TDT is an example of a conditional likelihood score test. The original TDT (Spielman *et al.* 1993) ascertains families which have one affected offspring and two heterozygous parents. In the conditional likelihood framework this is equivalent to assuming $r = 1, s = 0$ and the parental mating type $G = Aa \times Aa$. The Mendelian genotype transmission probabilities are $\tau_{G2} = P\{C = AA|G = Aa \times Aa\} = \frac{1}{4}$, $\tau_{G1} = P\{C = Aa|G = Aa \times Aa\} = \frac{1}{2}$, and $\tau_{G0} = P\{C = aa|G = Aa \times Aa\} = \frac{1}{4}$. Under the additive genetic model, the conditional score computed from (4) is

$$U_{Add} = \frac{1}{2f_0}(J_2 - J_0). \quad (14)$$

where $J_2 = \sum_{i=1}^N j_{2i}$, $J_1 = \sum_{i=1}^N j_{1i}$, $J_0 = \sum_{i=1}^N j_{0i}$, and $N = J_2 + J_1 + J_0$ families. Under the H_0, (J_2, J_1, J_0) has a trinomial distribution $(N; \frac{1}{4}, \frac{1}{2}, \frac{1}{4})$. Hence,

$$V^*_{Add} = Var_{H_0}(U_{Add}) = \frac{1}{4f_0^2}\frac{N}{2},$$

which also follows directly from the definition of V^*_{Add} following equation (5). Thus,

$$(T^*_{Add})^2 = \frac{(J_2-J_0)^2}{\frac{1}{2}N} = \frac{(2J_2-2J_0)^2}{2N}. \quad (15)$$

The statistics (15) is the TDT statistic. Under the original TDT ascertainment scheme and the multiplicative genetic model, $f_2 = \gamma^2 f_0$ and $f_1 = \gamma f_0$, the conditional likelihood score test described here also gives rise to the TDT (Spielman *et al.* 1993) as noted in Clayton & Jones (1999). The conditional likelihood score test statistics for the dominant and recessive models can be derived similarly. They differ from the TDT statistic, which is not an optimal test for dominant and recessive genetic models (Schaid & Sommer, 1993; Ewens & Spielman, 1995).

Conditional Fisher Information of the Conditional Likelihood of the Different Parental Mating Types

We use the conditional Fisher information, given the parental mating type, to investigate the informativeness of different parental mating types under various genetic models. Under each model, the conditional Fisher information given parental mating type is

$$I_G(f_2) = -E\left\{\frac{\partial^2 \log h_G^A h_G^U}{\partial f_2^2}\middle| G\right\} = I_G^A(f_2) + I_G^U(f_2),$$

which is shown in Table 2 for additive, dominant and recessive models. Here we use G to denote parental mating type, rather than joint parental genotypes.

The conditional likelihood, $h_G^A h_G^U$, describes the genotype transmission from parents to offspring and the affection status of the offspring. All offspring of doubly homozygous parents have the same genotype. For example, for the mating type $G = AA \times AA$, $\tau_{G2} = 1$ and $\tau_{G1} = \tau_{G0} = 0$. Thus, the conditional likelihood $h_G^A h_G^U$ is identical to one and the conditional Fisher information is zero.

Under the additive genetic model, the conditional Fisher information of doubly heterozygous parents is twice that of singly heterozygous parents when H_0 holds. When the baseline penetrance f_0 is less than $\frac{1}{2}$ and H_0 is true, the conditional Fisher information of h_G^A is greater than that of h_G^U. This means that a family with two affected children is more informative than another family with one affected and one unaffected child. However, the unaffected offspring do provide information, and failing to account for their ascertainment in family-based association studies leads to an incorrect conditional likelihood.

When the additive model holds, it is well known that the mating type $Aa \times Aa$ is most informative. If the disease follows a dominant model, there are only two informative mating types $Aa \times Aa$ and $Aa \times aa$. The results in Table 2 show that the $Aa \times aa$ mating type is more informative than the $Aa \times Aa$ mating type. Similarly, for the recessive model, the mating type $AA \times Aa$ is more informative than doubly heterozygous parents.

The original TDT is based on allele transmission (Spielman *et al.* 1993) from one parent to an affected child. A parent-child trio is treated as two independent parent-child pairs. If the parental mating type is $AA \times Aa$, the first parent is not informative while the second parent is informative. This corresponds to the fact that the conditional Fisher information of doubly heterozygous parents is approximately twice that of singly heterozygous parents under the additive model. The result that the mating type $AA \times Aa$ is more informative than the mating type $Aa \times Aa$ under the recessive model suggests that the two transmission processes

Table 2 Fisher Information in the Conditional Likelihood Given the Parental Mating Types for the Additive, Dominant and Recessive Genetic Models†

Informative Mating Type G	I_G^A		I_G^U	
	H_a	H_0‡	H_a	H_0
		Additive		
$AA \times Aa$	$\frac{2rf_0^2}{f_2(f_2+f_0)(3f_2+f_0)^2}$	$\frac{r}{16f_0^2}$	$\frac{2s(1-f_0)^2}{(1-f_2)(1-f_2+1-f_0)[3(1-f_0)+1-f_0]^2}$	$\frac{s}{16(1-f_0)^2}$
$Aa \times Aa$	$\frac{rf_0}{2f_2(f_2+f_0)^2}$	$\frac{r}{8f_0^2}$	$\frac{s(1-f_0)}{2(1-f_2)(1-f_2+1-f_0)^2}$	$\frac{s}{8(1-f_0)^2}$
$Aa \times aa$	$\frac{2rf_0}{(f_2+f_0)(f_2+3f_0)^2}$	$\frac{r}{16f_0^2}$	$\frac{2s(1-f_0)}{(1-f_2+1-f_0)[(1-f_2)+3(1-f_0)]^2}$	$\frac{s}{16(1-f_0)^2}$
		Dominant		
$Aa \times Aa$	$\frac{3rf_0}{f_2(3f_2+f_0)^2}$	$\frac{3r}{16f_0^2}$	$\frac{3s(1-f_0)}{(1-f_2)[3(1-f_2)+1-f_0]^2}$	$\frac{3s}{16(1-f_0)^2}$
$Aa \times aa$	$\frac{rf_0}{f_2(f_2+f_0)^2}$	$\frac{r}{4f_0^2}$	$\frac{s(1-f_0)}{(1-f_2+1-f_0)[(1-f_2)+(1-f_0)]^2}$	$\frac{s}{4(1-f_0)^2}$
		Recessive		
$AA \times Aa$	$\frac{rf_0}{f_2(f_2+f_0)^2}$	$\frac{r}{4f_0^2}$	$\frac{s(1-f_0)}{(1-f_2)(1-f_2+1-f_0)^2}$	$\frac{s}{4(1-f_0)^2}$
$Aa \times Aa$	$\frac{3rf_0}{f_2(f_2+3f_0)^2}$	$\frac{3r}{16f_0^2}$	$\frac{3s(1-f_0)}{(1-f_2)[1-f_2+3(1-f_0)]^2}$	$\frac{3s}{16(1-f_0)^2}$

†: Additive: $f_1 = \frac{f_2+f_0}{2}$; Dominant: $f_1 = f_2$; Recessive: $f_1 = f_0$. ‡: $H_0 : f_2 = f_0$.
Note that G denotes mating type in this table but joint parental genotypes in Table 1.

from two parents to the affected child should be considered jointly, as in the genotype transmission procedure developed here. Similarly, the mating type $AA \times Aa$ is non-informative while $aa \times Aa$ is informative under the dominant mode of inheritance. That is, whether or not a heterozygous parent is informative depends on the genotype of the other homozygous parent. Thus, especially for dominant or recessive models, or when the mode of inheritance is unknown, the analysis unit should be a trio consisting of two parents and one affected child, and the genotype based approach for analysis is preferable to an allele based approach.

Sample Sizes

To compute sample sizes from a formulae like (7), we need to compute mating type probabilities conditional on offspring phenotypes (Table 1). For this purpose we assume Hardy-Weinberg equilibrium, and we let p denote the frequency of the disease allele A.

Tables 3–5 give the total sample size, including the non-informative families that will be ascertained, needed to achieve 80% power for a level $\alpha = 5 \times 10^{-8}$.

Table 3a The Required Number of Families for 80% Power with a One-sided $\alpha = 5 \times 10^{-8}$ Level Test under an Additive Model, $r = 1$ Affected and $s = 0$ Unaffected Offspring

γ	$f_0 = 0.025$	$f_0 = 0.05$	$f_0 = 0.10$	$f_0 = 0.15$
		$p = 0.05$ (disease allele frequency)		
1.5	2926	2926	2926	2926
1.6	2025	2025	2025	2025
1.7	1488	1488	1488	1488
1.8	1143	1143	1143	1143
1.9	909	909	909	909
2.0	743	743	743	743
		$p = 0.2$		
1.5	1090	1090	1090	1090
1.6	788	788	788	788
1.7	605	605	605	605
1.8	485	485	485	485
1.9	402	402	402	402
2.0	342	342	342	342
		$p = 0.7$		
1.5	1518	1518	1518	1518
1.6	1202	1202	1202	1202
1.7	1002	1002	1002	1002
1.8	865	865	865	865
1.9	767	767	767	767
2.0	694	694	694	694

Table 3b The Required Number of Families for 80% Power with a One-sided $\alpha = 5 \times 10^{-8}$ Level Test under an Additive Model, $r = 1$ Affected and $s = 1$ Unaffected Offspring

γ	$f_0 = 0.025$	$f_0 = 0.05$	$f_0 = 0.10$	$f_0 = 0.15$
		$p = 0.05$ (disease allele frequency)		
1.5	2942	2952	2948	2900
1.6	2039	2049	2049	2017
1.7	1501	1510	1513	1489
1.8	1155	1163	1168	1149
1.9	919	927	933	917
2.0	752	760	765	752
		$p = 0.2$		
1.5	1092	1091	1078	1045
1.6	790	789	779	752
1.7	606	606	596	573
1.8	486	485	476	455
1.9	403	402	393	372
2.0	342	341	333	312
		$p = 0.7$		
1.5	1508	1491	1433	1332
1.6	1192	1176	1119	1022
1.7	991	974	918	820
1.8	854	837	778	678
1.9	756	738	677	571
2.0	682	663	598	486

Table 3c The Required Number of Families for 80% Power with a One-sided $\alpha = 5 \times 10^{-8}$ Level Test under an Additive Model, $r = 2$ Affected and $s = 1$ Unaffected Offspring

γ	$f_0 = 0.025$	$f_0 = 0.05$	$f_0 = 0.10$	$f_0 = 0.15$
		$p = 0.05$ (disease allele frequency)		
1.5	1195	1201	1208	1207
1.6	799	804	811	812
1.7	569	573	579	580
1.8	425	428	434	435
1.9	329	332	337	338
2.0	263	265	269	271
		$p = 0.2$		
1.5	502	503	500	493
1.6	362	362	360	354
1.7	278	278	276	270
1.8	224	223	221	215
1.9	186	186	183	177
2.0	159	159	156	149
		$p = 0.7$		
1.5	841	834	811	774
1.6	677	670	647	609
1.7	573	565	541	501
1.8	502	493	467	424
1.9	450	441	413	366
2.0	412	402	372	319

Table 3d The Required Number of Families for 80% Power with a One-sided $\alpha = 5 \times 10^{-8}$ Level Test under an Additive Model, $r = 1$ Affected and $s = 2$ Unaffected Offspring

γ	$f_0 = 0.025$	$f_0 = 0.05$	$f_0 = 0.10$	$f_0 = 0.15$
		$p = 0.05$ (disease allele frequency)		
1.5	2958	2979	2972	2885
1.6	2053	2073	2076	2017
1.7	1513	1532	1540	1498
1.8	1166	1183	1194	1163
1.9	930	946	959	935
2.0	762	777	791	772
		$p = 0.2$		
1.5	1094	1092	1067	1008
1.6	792	790	770	722
1.7	608	606	589	548
1.8	487	486	470	433
1.9	403	402	387	352
2.0	343	341	326	294
		$p = 0.7$		
1.5	1498	1465	1355	1180
1.6	1182	1150	1044	880
1.7	981	948	844	685
1.8	843	810	704	547
1.9	744	710	601	443
2.0	670	634	520	361

Table 4b The Required Number of Families for 80% Power with a One-sided $\alpha = 5 \times 10^{-8}$ Level Test under a Dominant Model, $r = 1$ Affected and $s = 1$ Unaffected Offspring

γ	$f_0 = 0.025$	$f_0 = 0.05$	$f_0 = 0.10$	$f_0 = 0.15$
		$p = 0.05$ (disease allele frequency)		
1.5	1008	1015	1021	1005
1.6	729	736	742	730
1.7	558	565	571	562
1.8	446	452	458	450
1.9	368	374	380	373
2.0	311	317	323	316
		$p = 0.2$		
1.5	478	477	468	448
1.6	362	361	353	335
1.7	289	288	281	263
1.8	241	239	232	215
1.9	206	205	197	180
2.0	181	180	172	153
		$p = 0.7$		
1.5	1746	1719	1632	1491
1.6	1400	1373	1287	1148
1.7	1179	1151	1063	921
1.8	1026	997	905	756
1.9	916	885	788	629
2.0	833	800	696	525

Table 4a The Required Number of Families for 80% Power with a One-sided $\alpha = 5 \times 10^{-8}$ Level Test under a Dominant Model, $r = 1$ Affected and $s = 0$ Unaffected Offspring

γ	$f_0 = 0.025$	$f_0 = 0.05$	$f_0 = 0.10$	$f_0 = 0.15$
		$p = 0.05$ (disease allele frequency)		
1.5	997	997	997	997
1.6	719	719	719	719
1.7	550	550	550	550
1.8	438	438	438	438
1.9	360	360	360	360
2.0	304	304	304	304
		$p = 0.2$		
1.5	477	477	477	477
1.6	361	361	361	361
1.7	289	289	289	289
1.8	241	241	241	241
1.9	207	207	207	207
2.0	181	181	181	181
		$p = 0.7$		
1.5	1765	1765	1765	1765
1.6	1420	1420	1420	1420
1.7	1198	1198	1198	1198
1.8	1047	1047	1047	1047
1.9	937	937	937	937
2.0	855	855	855	855

Table 5a The Required Number of Families for 80% Power with a One-sided $\alpha = 5 \times 10^{-8}$ Level Test under a Recessive Model, $r = 1$ Affected and $s = 0$ Unaffected Offspring

γ	$f_0 = 0.025$	$f_0 = 0.05$	$f_0 = 0.10$	$f_0 = 0.15$
		$p = 0.05$ (disease allele frequency)		
1.5	18986	18986	18986	18986
1.6	13063	13063	13063	13063
1.7	9532	9532	9532	9532
1.8	7263	7263	7263	7263
1.9	5721	5721	5721	5721
2.0	4627	4627	4627	4627
		$p = 0.2$		
1.5	1446	1446	1446	1446
1.6	1010	1010	1010	1010
1.7	748	748	748	748
1.8	579	579	579	579
1.9	463	463	463	463
2.0	380	380	380	380
		$p = 0.7$		
1.5	449	449	449	449
1.6	342	342	342	342
1.7	276	276	276	276
1.8	231	231	231	231
1.9	200	200	200	200
2.0	177	177	177	177

Table 5b The Required Number of Families for 80% Power with a One-sided $\alpha = 5 \times 10^{-8}$ Level Test under a Recessive Model, $r = 1$ Affected and $s = 1$ Unaffected Offspring

γ	$f_0 = 0.025$	$f_0 = 0.05$	$f_0 = 0.10$	$f_0 = 0.15$
		$p = 0.05$ (disease allele frequency)		
1.5	19125	19226	19277	19049
1.6	13184	13279	13356	13223
1.7	9640	9729	9819	9741
1.8	7362	7445	7542	7499
1.9	5812	5891	5992	5972
2.0	4712	4788	4890	4886
		$p = 0.2$		
1.5	1456	1463	1464	1442
1.6	1018	1025	1028	1013
1.7	756	762	766	755
1.8	586	591	596	588
1.9	469	475	480	473
2.0	386	391	396	391
		$p = 0.7$		
1.5	446	441	427	402
1.6	340	335	322	299
1.7	273	269	255	233
1.8	228	224	211	189
1.9	197	192	179	156
2.0	173	169	154	131

This level was chosen to be consistent with Risch & Teng (1998) to control the false positive rate in a genome scan. The focus is on diseases with low baseline penetrance (f_0). For each genetic model the number of families with $r(s)$ affected (unaffected) sibs is given. The relative risk $f_2/f_0 = \gamma^2$ ranges from 2.25 for $\gamma = 1.5$ to 4 for $\gamma = 2.0$.

Recessive models (Table 5) require larger samples than additive ones for $p \leq 0.2$ and smaller samples for $p = 0.7$ (Table 3). Dominant models tend to require the smallest samples except when p is large (Table 4). In families with no unaffected sibs ($s = 0$) sample sizes do not depend on f_0, and for families with one affected sib ($r = 1$) there is little dependence on f_0, regardless of the number of unaffected offspring. As shown in Table 3c and in similar unreported tables for dominant and recessive models, studies of families with two affected offspring ($r = 2$) require substantially smaller samples than those of families with one affected offspring ($r = 1$). Required sample sizes decrease monotonically with disease allele frequency for recessive models. For additive and dominant models, required sample sizes increase for small ($p = 0.05$) or large ($p = 0.7$) disease allele frequencies.

Discussion

We present explicit formulae for the conditional distribution of parental mating types given offspring phenotypes, and for the conditional distribution of offspring genotypes given parental genotypes and offspring affection status. This latter conditional distribution has been discussed by Clayton (1999), Clayton & Jones (1999), Whittemore & Tu (2000) and Shih & Whittemore (2002), and recommended because the size of the conditional score test is robust to population stratification in the case of the full parental genotype information that we consider. The likelihood is based on the assumption that familial phenotypes are conditionally independent given the individual family members' genotypes. We present sample sizes needed for families with one or two affected offspring and for 0, 1 or 2 unaffected offspring. These calculations indicate that it is hardly feasible to detect mutations associated with rare recessive disorders, whereas evaluation of about 1000 families will often yield sufficient power to detect associations for genes with a dominant or additive mode of inheritance and modest allele frequency. Compared to the dominant model, larger samples are needed for the additive model for moderate allele frequencies.

Our sample size calculations should agree with those of Chen & Deng (2001) in the case of $r = 1$ affected and $s = 0$ unaffected offspring. We used a computer program downloaded from Dr. Deng's website to check our calculations for the additive model. For allele frequency $P(A) = 0.05$, $f_0 = 0.05$, $f_1 = 0.125$ and $f_2 = 0.20$, we calculated that 743 families were needed to a obtain power of 0.8 for a one-sided $\alpha = 5 \times 10^{-8}$ level test, whereas the program for the procedure of Chen & Deng (2001) with two-sided $\alpha = 1 \times 10^{-7}$ yields 731. For $r = 1$, $s = 2$, $f_0 = 0.15$, $f_1 = 0.375$, $f_2 = 0.6$, however, with other parameters as above, we calculated that 772 families were required, compare to 911 families from the Chen & Deng program. In a personal communication, Dr. Deng clarified that the test for which he computed power put a weight of one on affected offspring and zero on unaffected offspring. Thus, for $s > 0$ our sample size calculations are more appropriate for statistics like (5), (9) and (12) than those by Chen & Deng (2001). Lange & Laird (2000a, 2000b) described power calculations for FBAT tests,

which should be equivalent to our tests when parental genotype are known. Software at the FBAT web page, http://www.biostat.harvard.edu/~fbat/default.html, indicates that sample size for FBAT can be computed subject to the restriction $s \leq 1$ unaffected offspring. We were surprised that the results from this program were very different from ours for dominant and recessive models. For example, for a recessive model with disease allele frequency $P(A) = 0.2$, $f_0 = 0.05$, $f_1 = 0.05$ and $f_2 = 0.2, \alpha = 5 \times 10^{-8}$, with $r = 1$ affected and $s = 0$ unaffected offspring, our calculations indicated that 380 families yielded power of 0.8, a result confirmed by simulation, whereas the FBAT program yielded a power of 0.0576 for 380 families.

If one chooses a statistic that does not correspond to the true mode of inheritance, power losses can be substantial. In the previous example of a recessive disease, the simulated power for the correct recessive score test was 0.8288, whereas the simulated power for the additive score test was only 0.0824. If the mode of inheritance is unknown, one could use all three optimum tests (T^*_{Add}, T^*_{Dom}, T^*_{Rec}) with a Bonferroni correction. The efficiency robustness literature (Gastwirth, 1966; Whittemore & Tu, 1998; Gastwirth & Freidlin, 2000; Zheng *et al.* 2002) enables one to obtain a more powerful procedure. One needs to compute the null correlations of the optimum statistics for three modes of inheritance - additive, dominant, and recessive. From equations (4), (8), and (11), these are

$$\rho_{AD} = \frac{2(g_{11} + g_{(10)})}{\sqrt{(g_{(21)} + 2g_{11} + g_{(10)})(3g_{11} + 4g_{(10)})}}$$

$$\rho_{AR} = \frac{2(g_{11} + g_{(21)})}{\sqrt{(g_{(21)} + 2g_{11} + g_{(10)})(3g_{11} + 4g_{(21)})}}$$

$$\rho_{RD} = \frac{g_{11}}{\sqrt{(3g_{11} + 4g_{(10)})(3g_{11} + 4g_{(21)})}}. \qquad (16)$$

Here, ρ_{AD} is the correlation between the additive and dominant score test statistics, and ρ_{AR} and ρ_{RD} are defined similarly. These correlations are functions of unconditional mating probabilities. Under assumptions of Hardy-Weinberg equilibrium and random mating, they are in turn functions of the allele frequency (p). For $p = 0.05, 0.20, 0.70$ the corresponding correlations are: $\rho_{AD} = 0.98, 0.92, 0.60$; $\rho_{AR} = 0.26, 0.50, 0.87$; $\rho_{RD} = 0.06, 0.11, 0.13$.

From the numerical values of correlations, when all three models are plausible, the previous literature indicates that the maximum of the three optimal tests is the most powerful. Using the joint asymptotic normal distribution and the null correlations one can determine the critical values by simulation. When one could eliminate the dominant or recessive model, a simple linear combination (MERT), $R = \frac{1}{\sqrt{2(1+\rho_{12})}}(T_1 + T_2)$, where T_1 and T_2 are the remaining optimal test statistics and ρ_{12} is their null correlation, is the best. Further research is needed to obtain the increase in sample size needed when applying these procedures to insure good power against all scientifically plausible models.

Two factors that can affect these sample size calculations substantially include missing parental data and the use of markers rather than candidate disease loci. Large increases in sample size are required to compensate for the attenuation of signal that results when a marker in linkage disequilibrium with the disease locus is used instead of the disease locus itself (Abel & Muller-Myhsok, 1998; Tu & Whittemore, 1999; Whittaker & Morris, 2001). Residual familial correlation of phenotypes given genotypes probably has only a minor affect on power, as indicated by the findings of Shih & Whittemore (2002), who allowed for residual familial correlations of phenotypes. Although the level of the CLSTs is unaffected by population stratification, under the alternative hypothesis the expectations and variances of the conditional likelihood score tests depend on the conditional mating type probabilities ($m_{ij}^{(r,s)}$). Thus, the power of the conditional likelihood score tests may be affected by population stratification.

The calculations in this paper are for candidate disease loci, for which the assumption of conditional independence, used in Appendix A to derive the likelihood function, is reasonable. However, this assumption is not valid for markers (Martin *et al.* 1997). As just mentioned, if we study marker loci, rather than disease loci, the required sample sizes can be much larger, as was shown for the TDT test (Abel & Muller-Myhsok, 1998; Tu & Whittemore, 1999) and for population-based and discordant sib-pair case-control studies (Pferffer & Gail, 2003). Although our power calculations do not apply for markers, the scores U_{Add}, U_{Dom} and U_{Rec} remain unbiased for zero under the null hypothesis of no disease

association with the marker. Standardization by empirical estimates of the standard deviation of the scores across families therefore yields a valid test of the null hypothesis, analogous to the procedure in Martin *et al.* (1997).

To assess the effect of misspecification of f_0, we conducted simulations where families with one affected ($r = 1$) and one unaffected ($s = 1$) offspring are ascertained. When f_0 is misspecified both in the design phase, including the determination of the sample size needed to achieve a nominal power of, say, 0.80, and in the analysis, the effect on power can be considerable. A 50% underestimate of f_0 has negligible effect on sample size calculations and power for a dominant model with true $f_0 \leq 0.10$, $p \leq 0.20$ and $\gamma \leq 2$, but a 50% overestimate of f_0 reduces power to 0.73 with $f_0 = 0.10$, $p = 0.2$ and $\gamma = 2$ and to 0.43 with $f_0 = 0.15$, $p = 0.2$ and $\gamma = 2$ (unreported data). Under an additive model, the estimated sample size and power are even more robust to a 50% underestimate of f_0, but a 50% overestimate again leads to a perceptible underestimate of the sample size and a decrease in power from 0.8 to 0.76 when $f_0 = 0.10$, $p = 0.2$ and $\gamma = 2$. Under a recessive model with $\gamma = 2$, a 50% overestimate or underestimate of f_0 has negligible effects on power for $p \leq 0.2$, but with $p = 0.7$, a 50% underestimate of f_0 leads to power 0.87 for $f_0 = 0.10$ and to 0.92 for $f_0 = 0.15$, whereas a 50% overestimate of f_0 leads to a power of only 0.67 for $f_0 = 0.10$ and 0.35 for $f_0 = 0.15$. As the sample size is the number of families that need to be ascertained, which varies inversely with f_0, overestimation of f_0 leads to an underestimate of sample size and reduced power.

For diseases with population disease risk $f \leq 0.1$, it is adequate to set f_0 equal to f. The quantity f overestimates f_0, however. Indeed, for a dominant model $\frac{f}{f_0} = (1-p)^2 + [2p(1-p) + p^2]\gamma^2$, for an additive model $\frac{f}{f_0} = (1-p)^2 + 2p(1-p)\gamma + p^2\gamma^2$, and for a recessive model $\frac{f}{f_0} = (1-p)^2 + 2p(1-p) + p^2\gamma^2$. Thus, we recommend dividing the population risk, f, by the terms on the right hand sides of these expressions to estimate f_0 when f exceeds 0.10. A rather strong genetic effect of $\gamma = 2$ and fairly common variant allele frequency $p = 0.2$ requires dividing f by the factor 2.08 for a dominant model, by 1.44 for an additive model, and by 1.12 for a recessive model. Therefore the required sample sizes could be conservatively estimated by setting $f_0 = \frac{f}{2.08}$, but values of f_0 closer to f would be reasonable if segregation analyses are more consistent with additive or recessive models.

Although the choice of f_0 can have appreciable impact if the misspecified f_0 is used both to design and analyze the study, misspecification of f_0 has relatively little effect on the analysis of studies with sample sizes based on the correct f_0. For example, a 50% overestimate of f_0 has negligible impact on the analyses and power of such studies with $f_0 \leq 0.10$. For $f_0 = 0.15$, $p = 0.2$, and $\gamma = 2$, a 50% overestimate of f_0 in the analysis yields a power of 0.87 for the dominant model, rather than 0.43 reported above, which results when the over-estimated f_0 is used both to design and analyze the study.

We recommend a model-based variance estimate V^* for normalization of the conditional score statistics. If there is residual familial correlation of phenotypes given genotypes, one can use the empirical variance S^2 of the scores, which is robust to such residual correlation, as in Siegmund *et al.* (2000). In unreported simulations with samples of practical size, the size of the tests based on S^2 was near nominal levels, but the power sometimes approached 0.9, rather than the nominal power of 0.8 predicted by asymptotic theory, particularly for recessive models with rare alleles. On the other hand, for some dominant models the power was nearer 0.75 rather than the predicted 0.80. For this reason we have tabulated sample sizes based on V^*, which agree well with asymptotic theory. Sample size calculations for S^2 yield similar results to those in Tables 3–5. Software can be obtained by contacting the first author (zli@gwu.edu).

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Appendix A: Derivations of Likelihood Function (1)

$$
\begin{aligned}
&P\{j_2, j_1, j_0, k_2, k_1, k_0, G|C_{r_i} = \text{Aff}, C_{s_i} = \text{Unaff}\}\\
&\quad = \frac{1}{P\{G, C_{r_i} = \text{Aff}, C_{s_i} = \text{Unaff}\}}\\
&\quad \times P\{G|C_{r_i} = \text{Aff}, C_{s_i} = \text{Unaff}\}\\
&\quad \times P\{C_{r_i} = \text{Aff}, C_{s_i} = \text{Unaff}|j_2, j_1, j_0, k_2, k_1, k_0\}\\
&\quad \times P\{j_2, j_1, j_0, k_2, k_1, k_0|G\}\, P\{G\}\\
&\quad = \frac{m_G^{(r_i,s_i)}}{P\{G\}\, P\{C_{r_i} = \text{Aff}, C_{s_i} = \text{Unaff}|G\}}\\
&\quad \times \binom{r_i + s_i}{r_i}\binom{r_i}{j_2, j_1, j_0} f_2^{j_2} f_1^{j_1} f_0^{j_0}\\
&\quad \times \binom{s_i}{k_2, k_1, k_0}(1 - f_2)^{k_2}(1 - f_1)^{k_1}\\
&\quad \times (1 - f_0)^{k_0} P\{j_2, j_1, j_0, k_2, k_1, k_0|G\}\, P\{G\}
\end{aligned}
$$

where $m_G^{(r_i,s_i)} = P\{G|C_{r_i} = \text{Aff}, C_{s_i} = \text{Unaff}\}$ is the conditional mating probability. Using the conditional independence, we have

$$
\begin{aligned}
&P\{C_{r_i} = \text{Aff}, C_{s_i} = \text{Unaff}|G\}\\
&\quad = \binom{r_i + s_i}{r_i}(P\{C_1 = \text{Aff}|G\})^{r_i}\\
&\quad \times (P\{C_1 = \text{Unaff}|G\})^{s_i}\\
&\quad = \binom{r_i + s_i}{r_i}(P\{C_1 = \text{Aff}|C_1 = AA\}\\
&\quad \times P\{C_1 = AA|G\} + P\{C_1 = \text{Aff}|C_1 = Aa\}\\
&\quad \times P\{C_1 = Aa|G\} + P\{C_1 = \text{Aff}|C_1 = aa\}\\
&\quad \times P\{C_1 = aa|G\})^{r_i}\\
&\quad \times (P\{C_1 = \text{Unaff}|C_1 = AA\}\, P\{C_1 = AA|G\}\\
&\quad + P\{C_1 = \text{Unaff}|C_1 = Aa\}\, P\{C_1 = Aa|G\}\\
&\quad + P\{C_1 = \text{Unaff}|C_1 = aa\}\, P\{C_1 = aa|G\})^{s_i}\\
&\quad = \binom{r_i + s_i}{r_i}\left(\sum_{l=0}^{2}\tau_{Gl} f_l\right)^{r_i}\left(\sum_{l=0}^{2}\tau_{Gl}(1 - f_l)\right)^{s_i}
\end{aligned}
$$

where $\tau_{G2} = P\{C_1 = AA|G\}$, $\tau_{G1} = P\{C_1 = Aa|G\}$, and $\tau_{G0} = P\{C_1 = aa|G\}$, are the genotype transmission probabilities. We also have

$$P\{j_2, j_1, j_0, k_2, k_1, k_0|G\} = \tau_{G2}^{j_2}\tau_{G1}^{j_1}\tau_{G0}^{j_0}\tau_{G2}^{k_2}\tau_{G1}^{k_1}\tau_{G0}^{k_0}.$$

Hence,

$$
\begin{aligned}
&P\{j_2, j_1, j_0, k_2, k_1, k_0, G|C_{r_i} = \text{Aff}, C_{s_i} = \text{Unaff}\}\\
&\quad = m_G^{(r_i,s_i)}\binom{r_i}{j_2, j_1, j_0}\binom{s_i}{k_2, k_1, k_0}\left(\frac{\tau_{G2} f_2}{\sum_{l=0}^{2}\tau_{Gl} f_l}\right)^{j_2}\\
&\quad \times \left(\frac{\tau_{G1} f_1}{\sum_{l=0}^{2}\tau_{Gl} f_l}\right)^{j_1}\left(\frac{\tau_{G0} f_0}{\sum_{l=0}^{2}\tau_{Gl} f_l}\right)^{j_0}\\
&\quad \times \left(\frac{\tau_{G2}(1 - f_2)}{\sum_{l=0}^{2}\tau_{Gl}(1 - f_l)}\right)^{k_2}\left(\frac{\tau_{G1}(1 - f_1)}{\sum_{l=0}^{2}\tau_{Gl}(1 - f_l)}\right)^{k_1}\\
&\quad \times \left(\tau_{G0}(1 - f_0)\sum_{l=0}^{2}\tau_{Gl}(1 - f_l)\right)^{k_0}\\
&\quad = m_G^{(r_i,s_i)} h_G^A(j_2, j_1, j_0) h_G^U(k_2, k_1, k_0),
\end{aligned}
$$

where

$$h_G^A(j_2, j_1, j_0) = \binom{r_i}{j_2, j_1, j_0}\left(\frac{\tau_{G2} f_2}{\sum_{l=0}^{2}\tau_{Gl} f_l}\right)^{j_2} \times \left(\frac{\tau_{G1} f_1}{\sum_{l=0}^{2}\tau_{Gl} f_l}\right)^{j_1}\left(\frac{\tau_{G0} f_0}{\sum_{l=0}^{2}\tau_{Gl} f_l}\right)^{j_0},$$

$$h_G^U(k_2, k_1, k_0) = \binom{s_i}{k_2, k_1, k_0}\left(\frac{\tau_{G2}(1-f_2)}{\sum_{l=0}^{2}\tau_{Gl}(1-f_l)}\right)^{k_2} \times \left(\frac{\tau_{G1}(1-f_1)}{\sum_{l=0}^{2}\tau_{Gl}(1-f_l)}\right)^{k_1}\left(\frac{\tau_{G0}(1-f_0)}{\sum_{l=0}^{2}\tau_{Gl}(1-f_l)}\right)^{k_0}.$$

Appendix B: Formulas and Derivations of μ_{aAdd} and σ^2_{aAdd}

Assuming that $r_i = r$ and $s_i = s$, under the additive model the score test is

$$U_{Add} = \frac{1}{f_0(1-f_0)}\sum_{i=1}^{N} \times \left\{(1-f_0)\left[j_{2i} - r_i\tau_{G2} + \frac{1}{2}(j_{1i} - r_i\tau_{G1})\right] - f_0\left[k_{2i} - s_i\tau_{G2} + \frac{1}{2}(k_{1i} - s_i\tau_{G1})\right]\right\}$$

To express the expectation of the score under the alternative hypothesis, H_a, we require notation for the conditional expectations of the scores with respect to the affected offspring given the parental mating type:

$$\mu^{A2}_{G21a} = E_{H_a}\{(j_2 - r\tau_{G2})\,|\,G = (2,1)\} = r\left(\frac{2f_2}{3f_2 + f_0} - \frac{1}{2}\right),$$

$$\mu^{A2}_{G11a} = E_{H_a}\{(j_2 - r\tau_{G2})\,|\,G = (1,1)\} = r\left(\frac{f_2}{2(f_2 + f_0)} - \frac{1}{4}\right),$$

$$\mu^{A2}_{G10a} = E_{H_a}\{(j_2 - r\tau_{G2})\,|\,G = (1,0)\} = 0,$$

$$\mu^{A1}_{G21a} = E_{H_a}\{(j_1 - r\tau_{G1})\,|\,G = (2,1)\} = r\left(\frac{f_2 + f_0}{3f_2 + f_0} - \frac{1}{2}\right),$$

$$\mu^{A1}_{G11a} = E_{H_a}\{(j_1 - r\tau_{G1})\,|\,G = (1,1)\} = \frac{r}{2} - \frac{r}{2} = 0,$$

$$\mu^{A1}_{G10a} = E_{H_a}\{(j_1 - r\tau_{G1})\,|\,G = (1,0)\} = r\left(\frac{f_2 + f_0}{f_2 + 3f_0} - \frac{1}{2}\right).$$

The corresponding unconditional expectations are

$$\mu^{A2}_a = E_{H_a}(j_2 - r\tau_{G2}) = \mu^{A2}_{G21a} m^{(r,s)}_{(21)} + \mu^{A2}_{G11a} m^{(r,s)}_{11},$$

$$\mu^{A1}_a = E_{H_a}(j_1 - r\tau_{G1}) = \mu^{A1}_{G21a} m^{(r,s)}_{(21)} + \mu^{A1}_{G10a} m^{(r,s)}_{(10)}.$$

The conditional expectations for the unaffected offspring given parental mating type are:

$$\mu^{U2}_{G21a} = E_{H_a}\{(k_2 - s\tau_{G2})|\,G = (2,1)\} = s\left(\frac{2(1-f_2)}{3(1-f_2) + 1 - f_0} - \frac{1}{2}\right),$$

$$\mu^{U2}_{G11a} = E_{H_a}\{(k_2 - s\tau_{G2})|\,G = (1,1)\} = s\left(\frac{1-f_2}{2(1-f_2) + 2(1-f_0)} - \frac{1}{4}\right),$$

$$\mu^{U2}_{G10a} = E_{H_a}\{(k_2 - s\tau_{G2})|\,G = (1,0)\} = 0,$$

$$\mu^{U1}_{G21a} = E_{H_a}\{(k_1 - s\tau_{G1})|\,G = (2,1)\} = s\left(\frac{1-f_2+1-f_0}{3(1-f_2) + 1 - f_0} - \frac{1}{2}\right),$$

$$\mu^{U1}_{G11a} = E_{H_a}\{(k_1 - s\tau_{G1})|\,G = (1,1)\} = \frac{s}{2} - \frac{s}{2} = 0,$$

$$\mu^{U1}_{G10a} = E_{H_a}\{(k_1 - s\tau_{G1})|\,G = (1,0)\} = s\left(\frac{1-f_2+1-f_0}{(1-f_2) + 3(1-f_0)} - \frac{1}{2}\right).$$

The unconditional expectations are

$$\mu^{U2}_a = E_{H_a}(k_2 - s\tau_{G2}) = \mu^{U2}_{G21a} m^{(r,s)}_{(21)} + \mu^{U2}_{G11a} m^{(r,s)}_{11},$$

$$\mu^{U1}_a = E_{H_a}(k_1 - s\tau_{G1}) = \mu^{U1}_{G21a} m^{(r,s)}_{(21)} + \mu^{U1}_{G10a} m^{(r,s)}_{(10)}.$$

Thus,

$$E_{H_a}(U_{Add}) = \frac{N}{f_0(1-f_0)}\Big\{(1-f_0)E_{H_a}(j_2 - r\tau_{G2}) + \frac{1}{2}(1-f_0)E_{H_a}(j_1 - r\tau_{G1}) - f_0 E_{H_a}(k_2 - s\tau_{G2}) - \frac{1}{2}f_0 E_{H_a}(k_1 - s\tau_{G1})\Big\} = N\mu_{a\,Add},$$

where

$$\mu_{a\,Add} = \frac{1}{f_0(1-f_0)}\Big\{(1-f_0)\mu_a^{A2} + \frac{1}{2}(1-f_0)\mu_a^{A1} - f_0\mu_a^{U2} - \frac{1}{2}f_0\mu_a^{U1}\Big\}.$$

The conditional variances of the scores for the affected offspring are:

$$\sigma^{A2}_{G21a} = Var_{H_a}\{(j_2 - r\tau_{G2})|\,G = (2,1)\} = rr\,\frac{2f_2(f_2+f_0)}{(3f_2+f_0)^2},$$

$$\sigma^{A2}_{G11a} = Var_{H_a}\{(j_2 - r\tau_{G2})|\,G = (1,1)\} = rr\,\frac{f_2(f_2+2f_0)}{[2(f_2+f_0)]^2},$$

$$\sigma^{A2}_{G10a} = Var_{H_a}\{(j_2 - r\tau_{G2})|\,G = (1,0)\} = 0,$$

$$\sigma^{A1}_{G21a} = Var_{H_a}\{(j_1 - r\tau_{G1})|\,G = (2,1)\} = rr\,\frac{2f_2(f_2+f_0)}{(3f_2+f_0)^2},$$

$$\sigma^{A1}_{G11a} = Var_{H_a}\{(j_1 - r\tau_{G1})|\,G = (1,1)\} = r\frac{r}{4},$$

$$\sigma^{A1}_{G10a} = Var_{H_a}\{(j_1 - r\tau_{G1})|\,G = (1,0)\} = rr\,\frac{2f_0(f_2+f_0)}{(f_2+3f_0)^2}.$$

The variances of the scores for the affected offspring are:

$$\sigma_a^{A2} = Var_{H_a}(j_2 - r\tau_{G2}) = Var(E_{H_a}\{(j_2 - r\tau_{G2})|\,G\}) + E(Var_{H_a}\{(j_2 - r\tau_{G2})|\,G\}) = \left(\mu^{A2}_{G21a}\right)^2 m^{(r,s)}_{(21)} + \left(\mu^{A2}_{G11a}\right)^2 m^{(r,s)}_{11} - \left[\mu^{A2}_{G21a}m^{(r,s)}_{(21)} + \mu^{A2}_{G11a}m^{(r,s)}_{11}\right]^2 + \sigma^{A2}_{G21a}m^{(r,s)}_{(21)} + \sigma^{A2}_{G11a}m^{(r,s)}_{11},$$

$$\sigma_a^{A1} = Var_{H_a}(j_1 - r\tau_{G1}) = Var(E_{H_a}\{(j_1 - r\tau_{G1})|\,G\}) + E(Var_{H_a}\{(j_1 - r\tau_{G1})|\,G\}) = \left(\mu^{A1}_{G21a}\right)^2 m^{(r,s)}_{(21)} + \left(\mu^{A1}_{G10a}\right)^2 m^{(r,s)}_{(10)} - \left[\mu^{A1}_{G21a}m^{(r,s)}_{(21)} + \mu^{A1}_{G10a}m^{(r,s)}_{(10)}\right]^2 + \sigma^{A1}_{G21a}m^{(r,s)}_{(21)} + \frac{r}{4}m^{(r,s)}_{11} + \sigma^{A1}_{G10a}m^{(r,s)}_{(10)}.$$

The conditional variances of the scores for unaffected offspring are:

$$\sigma^{U2}_{G21a} = Var_{H_a}\{(k_2 - s\tau_{G2})|\,G = (2,1)\} = s\,\frac{2(1-f_2)(1-f_2+1-f_0)}{[3(1-f_2)+1-f_0]^2},$$

$$\sigma^{U2}_{G11a} = Var_{H_a}\{(k_2 - s\tau_{G2})|\,G = (1,1)\} = s\,\frac{(1-f_2)(1-f_2+2(1-f_0))}{[2(1-f_2)+2(1-f_0)]^2},$$

$$\sigma^{U2}_{G10a} = Var_{H_a}\{(k_2 - s\tau_{G2})|\,G = (1,0)\} = 0,$$

$$\sigma^{U1}_{G21a} = Var_{H_a}\{(k_1 - s\tau_{G1})|\,G = (2,1)\} = s\,\frac{2(1-f_2)(1-f_2+1-f_0)}{[3(1-f_2)+1-f_0]^2},$$

$$\sigma^{U1}_{G11a} = Var_{H_a}\{(k_1 - s\tau_{G1})|\,G = (1,1)\} = \frac{s}{4},$$

$$\sigma^{U1}_{G10a} = Var_{H_a}\{(k_1 - s\tau_{G1})|\,G = (1,0)\} = s\,\frac{2(1-f_0)(1-f_2+1-f_0)}{[1-f_2+3(1-f_0)]^2}.$$

The variances of the score of unaffected offspring are:

$$\sigma_a^{U2} = Var_{H_a}(k_2 - s\tau_{G2}) = Var(E_{H_a}\{(k_2 - s\tau_{G2})|\,G\}) + E(Var_{H_a}\{(k_2 - s\tau_{G2})|\,G\}) = \left(\mu^{U2}_{G21a}\right)^2 m^{(r,s)}_{(21)} + \left(\mu^{U2}_{G11a}\right)^2 m^{(r,s)}_{11} - \left[\mu^{U2}_{G21a}m^{(r,s)}_{(21)} + \mu^{U2}_{G11a}m^{(r,s)}_{11}\right]^2 + \sigma^{U2}_{G21a}m^{(r,s)}_{(21)} + \sigma^{U2}_{G11a}m^{(r,s)}_{11},$$

$$\begin{aligned}\sigma_a^{U1} &= Var_{H_a}(k_1 - s\tau_{G1}) \\ &= Var\left(E_{H_a}\{(k_1 - s\tau_{G1})|G\}\right) \\ &\quad + E\left(Var_{H_a}\{(k_1 - s\tau_{G1})|G\}\right) \\ &= \left(\mu_{G21a}^{U1}\right)^2 m_{(21)}^{(r,s)} + \left(\mu_{G10a}^{U1}\right)^2 m_{(10)}^{(r,s)} \\ &\quad - \left[\mu_{G21a}^{U1} m_{(21)}^{(r,s)} + \mu_{G10a}^{U1} m_{(10)}^{(r,s)}\right]^2 \\ &\quad + \sigma_{G21a}^{U1} m_{(21)}^{(r,s)} + \tfrac{s}{4} m_{11}^{(r,s)} + \sigma_{G10a}^{U1} m_{(10)}^{(r,s)}.\end{aligned}$$

The six covariance terms are:

$$\begin{aligned}\sigma_a^{A21} &= Cov_{H_a}(j_2 - r\tau_{G2}, j_1 - r\tau_{G1}) \\ &= \left[r(r-1)\frac{2f_2(f_2+f_0)}{(3f_2+f_0)^2} - \frac{r^2}{4}\right] m_{(21)}^{(r,s)} \\ &\quad - \frac{rf_2}{4(f_2+f_0)} m_{11}^{(r,s)} - \mu_a^{A2}\mu_a^{A1},\end{aligned}$$

$$\begin{aligned}\sigma_a^{U21} &= Cov_{H_a}(k_2 - s\tau_{G2}, k_1 - s\tau_{G1}) \\ &= \left[s(s-1)\frac{2(1-f_2)(1-f_2+1-f_0)}{(3(1-f_2)+1-f_0)^2} \right. \\ &\quad \left. - \frac{s^2}{4}\right] m_{(21)}^{(r,s)} \\ &\quad - \frac{s(1-f_2)}{4(1-f_2)+4(1-f_0)} m_{11}^{(r,s)} - \mu_a^{U2}\mu_a^{U1},\end{aligned}$$

$$\begin{aligned}\sigma_a^{A2U2} &= Cov_{H_a}(j_2 - r\tau_{G2}, k_2 - s\tau_{G2}) \\ &= \mu_{G21a}^{A2}\mu_{G21a}^{U2} m_{(21)}^{(r,s)} + \mu_{G11a}^{A2}\mu_{G11a}^{U2} m_{11}^{(r,s)} \\ &\quad - \mu_a^{A2}\mu_a^{U2},\end{aligned}$$

$$\begin{aligned}\sigma_a^{A2U1} &= Cov_{H_a}(j_2 - r\tau_{G2}, k_1 - s\tau_{G1}) \\ &= \mu_{G21a}^{A2}\mu_{G21a}^{U1} m_{(21)}^{(r,s)} - \mu_a^{A2}\mu_a^{U1},\end{aligned}$$

$$\begin{aligned}\sigma_a^{A1U2} &= Cov_{H_a}(j_1 - r\tau_{G1}, k_2 - s\tau_{G2}) \\ &= \mu_{G21a}^{A1}\mu_{G21a}^{U2} m_{(21)}^{(r,s)} - \mu_a^{A1}\mu_a^{U2},\end{aligned}$$

$$\begin{aligned}\sigma_a^{A1U1} &= Cov_{H_a}(j_1 - r\tau_{G1}, k_1 - s\tau_{G1}) \\ &= \mu_{G21a}^{A1}\mu_{G21a}^{U1} m_{(21)}^{(r,s)} + \mu_{G10a}^{A1}\mu_{G10a}^{U1} m_{(10)}^{(r,s)} \\ &\quad - \mu_a^{A1}\mu_a^{U1}.\end{aligned}$$

The variance of the score statistic under the additive genetic model and alternative hypothesis is given by

$$Var_{H_a}(U_{Add}) = N\sigma_{a\,Add}^2,$$

where

$$\begin{aligned}\sigma_{a\,Add}^2 &= \frac{1}{f_0^2(1-f_0)^2}\left\{(1-f_0)^2\sigma_a^{A2} + \frac{1}{4}(1-f_0)^2\sigma_a^{A1}\right. \\ &\quad + (1-f_0)^2\sigma_a^{A21} \\ &\quad + f_0^2\sigma_a^{U2} + \frac{1}{4}f_0^2\sigma_a^{U1} + f_0^2\sigma_a^{U21} \\ &\quad - 2(1-f_0)f_0\sigma_a^{A2U2} \\ &\quad - (1-f_0)f_0\sigma_a^{A2U1} - (1-f_0)f_0\sigma_a^{A1U2} \\ &\quad \left. - \frac{1}{2}(1-f_0)f_0\sigma_a^{A1U1}\right\}.\end{aligned}$$

Appendix C: Formulae for the Dominant Model

$$\begin{aligned}\mu_{a\,Dom} &= \frac{r}{f_0}\left[\left(\frac{3f_2}{3f_2+f_0} - \frac{3}{4}\right) m_{11}^{(r,s)} \right. \\ &\quad \left. + \left(\frac{f_2}{f_2+f_0} - \frac{1}{2}\right) m_{(10)}^{(r,s)}\right] \\ &\quad - \frac{s}{1-f_0}\left[\left(\frac{3(1-f_2)}{3(1-f_2)+1-f_0} - \frac{3}{4}\right) m_{11}^{(r,s)} \right. \\ &\quad \left. + \left(\frac{1-f_2}{1-f_2+1-f_0} - \frac{1}{2}\right) m_{(10)}^{(r,s)}\right].\end{aligned}$$

$$Var_{H_a}(U_{Dom}) = N\sigma_{a\,Dom}^2,$$

where

$$\begin{aligned}\sigma_{a\,Dom}^2 &= \frac{1}{f_0^2} Var_{H_a}[j_2 + j_1 - r(\tau_{G2} + \tau_{G1})] \\ &\quad + \frac{1}{(1-f_0)^2} Var_{H_a}[k_2 + k_1 - s(\tau_{G2} + \tau_{G1})] \\ &\quad - \frac{2}{f_0(1-f_0)} Cov_{H_a}[j_2 + j_2 - r(\tau_{G2} + \tau_{G1}), \\ &\quad k_2 + k_1 - s(\tau_{G2} + \tau_{G1})].\end{aligned}$$

The variances and covariance in the above formula are given by

$$
\begin{aligned}
&Var_{H_a}[j_2 + j_1 - r(\tau_{G2} + \tau_{G1})] \\
&\quad = r^2\left(\frac{3f_2}{3f_2 + f_0} - \frac{3}{4}\right)^2 m_{11}^{(r,s)} \\
&\qquad + r^2\left(\frac{f_2}{f_2 + f_0} - \frac{1}{2}\right)^2 m_{(10)}^{(r,s)} \\
&\qquad - r^2\left[\left(\frac{3f_2}{3f_2 + f_0} - \frac{3}{4}\right)m_{11}^{(r,s)}\right. \\
&\qquad \left. + \left(\frac{f_2}{f_2 + f_0} - \frac{1}{2}\right)m_{(10)}^{(r,s)}\right]^2 \\
&\qquad + r\,\frac{3f_2 f_0}{(3f_2 + f_0)^2} m_{11}^{(r,s)} + r\,\frac{f_2 f_0}{(f_2 + f_0)^2} m_{(10)}^{(r,s)},
\end{aligned}
$$

$$
\begin{aligned}
&Var_{H_a}[k_2 + k_1 - s(\tau_{G2} + \tau_{G1})] \\
&\quad = s^2\left(\frac{3(1 - f_2)}{3(1 - f_2) + 1 - f_0} - \frac{3}{4}\right)^2 m_{11}^{(r,s)} \\
&\qquad + s^2\left(\frac{1 - f_2}{1 - f_2 + 1 - f_0} - \frac{1}{2}\right)^2 m_{(10)}^{(r,s)} \\
&\qquad - s^2\left[\left(\frac{3(1 - f_2)}{3(1 - f_2) + 1 - f_0} - \frac{3}{4}\right)m_{11}^{(r,s)}\right. \\
&\qquad \left. + \left(\frac{1 - f_2}{1 - f_2 + 1 - f_0} - \frac{1}{2}\right)m_{(10)}^{(r,s)}\right]^2 \\
&\qquad + s\,\frac{3(1 - f_2)(1 - f_0)}{(3(1 - f_2) + 1 - f_0)^2} m_{11}^{(r,s)} \\
&\qquad + s\,\frac{(1 - f_2)(1 - f_0)}{(1 - f_2 + 1 - f_0)^2} m_{(10)}^{(r,s)},
\end{aligned}
$$

$$
\begin{aligned}
&Cov_{H_a}[j_2 + j_1 - r(\tau_{G2} + \tau_{G1}), \\
&\quad k_2 + k_1 - s(\tau_{G2} + \tau_{G1})] \\
&\quad = rs\left(\frac{3f_2}{3f_2 + f_0} - \frac{3}{4}\right) \\
&\qquad \times \left(\frac{3(1 - f_2)}{3(1 - f_2) + 1 - f_0} - \frac{3}{4}\right)m_{11}^{(r,s)} \\
&\qquad + rs\left(\frac{f_2}{f_2 + f_0} - \frac{1}{2}\right) \\
&\qquad \times \left(\frac{1 - f_2}{1 - f_2 + 1 - f_0} - \frac{1}{2}\right)m_{(10)}^{(r,s)} \\
&\qquad - rs\left[\left(\frac{3f_2}{3f_2 + f_0} - \frac{3}{4}\right)m_{11}^{(r,s)}\right. \\
&\qquad \left. + \left(\frac{f_2}{f_2 + f_0} - \frac{1}{2}\right)m_{(10)}^{(r,s)}\right] \\
&\qquad \times \left[\left(\frac{3(1 - f_2)}{3(1 - f_2) + 1 - f_0} - \frac{3}{4}\right)m_{11}^{(r,s)}\right. \\
&\qquad \left. + \left(\frac{1 - f_2}{1 - f_2 + 1 - f_0} - \frac{1}{2}\right)m_{(10)}^{(r,s)}\right].
\end{aligned}
$$

Appendix D: Formulae for the Recessive Model

$$
\begin{aligned}
\mu_{a\,Rec} &= \frac{r}{f_0}\left[\left(\frac{f_2}{f_2 + f_0} - \frac{1}{2}\right)m_{(21)}^{(r,s)}\right. \\
&\quad \left. + \left(\frac{f_2}{f_2 + 3f_0} - \frac{1}{4}\right)m_{11}^{(r,s)}\right] \\
&\quad - \frac{s}{1 - f_0}\left[\left(\frac{1 - f_2}{1 - f_2 + 1 - f_0} - \frac{1}{2}\right)m_{(21)}^{(r,s)}\right. \\
&\quad \left. + \left(\frac{1 - f_2}{1 - f_2 + 3(1 - f_0)} - \frac{1}{4}\right)m_{11}^{(r,s)}\right].
\end{aligned}
$$

Likewise,

$$Var_{H_a}(U_{Rec}) = N\sigma_{a\,Rec}^2.$$

where

$$
\begin{aligned}
\sigma_{a\,Rec}^2 &= \frac{1}{f_0^2} Var_{H_a}(j_2 - r\tau_{G2}) \\
&\quad + \frac{1}{(1 - f_0)^2} Var_{H_a}(k_2 - s\tau_{G2}) \\
&\quad - \frac{2}{f_0(1 - f_0)} Cov_{H_a}(j_2 - r\tau_{G2}, k_2 - s\tau_{G2}),
\end{aligned}
$$

$$
\begin{aligned}
&Var_{H_a}(j_2 - r\tau_{G2}) = r^2\left(\frac{f_2}{f_2 + f_0} - \frac{1}{2}\right)^2 m_{(21)}^{(r,s)} \\
&\quad + r^2\left(\frac{f_2}{f_2 + 3f_0} - \frac{1}{4}\right)^2 m_{11}^{(r,s)} \\
&\quad - r^2\left[\left(\frac{f_2}{f_2 + f_0} - \frac{1}{2}\right)m_{(21)}^{(r,s)}\right. \\
&\quad \left. + \left(\frac{f_2}{f_2 + 3f_0} - \frac{1}{4}\right)m_{11}^{(r,s)}\right]^2 \\
&\quad + r\,\frac{f_2 f_0}{(f_2 + f_0)^2} m_{(21)}^{(r,s)} + r\,\frac{3f_2 f_0}{(f_2 + 3f_0)^2} m_{11}^{(r,s)},
\end{aligned}
$$

$$
\begin{aligned}
Var_{H_a}(k_2 - s\tau_{G2}) = {} & s^2\left(\frac{1-f_2}{1-f_2+1-f_0} - \frac{1}{2}\right)^2 m_{(21)}^{(r,s)} \\
& + s^2\left(\frac{1-f_2}{1-f_2+3(1-f_0)} - \frac{1}{4}\right)^2 m_{11}^{(r,s)} \\
& - s^2\left[\left(\frac{1-f_2}{1-f_2+1-f_0} - \frac{1}{2}\right)m_{(21)}^{(r,s)}\right. \\
& \left. + \left(\frac{1-f_2}{1-f_2+3(1-f_0)} - \frac{1}{4}\right)m_{11}^{(r,s)}\right]^2 \\
& + s\,\frac{(1-f_2)(1-f_0)}{(1-f_2+1-f_0)^2} m_{(21)}^{(r,s)} \\
& + s\,\frac{3(1-f_2)(1-f_0)}{(1-f_2+3(1-f_0))^2} m_{11}^{(r,s)},
\end{aligned}
$$

$$
\begin{aligned}
Cov_{H_a}(j_2 - r\tau_{G2}, k_2 - s\tau_{G2}) = {} & rs\left(\frac{f_2}{f_2+f_0} - \frac{1}{2}\right) \\
& \times \left(\frac{1-f_2}{1-f_2+1-f_0} - \frac{1}{2}\right)m_{(21)}^{(r,s)}. \\
& + rs\left(\frac{f_2}{f_2+3f_0} - \frac{1}{4}\right) \\
& \times \left(\frac{1-f_2}{1-f_2+3(1-f_0)} - \frac{1}{4}\right)m_{11}^{(r,s)} \\
& - rs\left[\left(\frac{f_2}{f_2+f_0} - \frac{1}{2}\right)m_{(21)}^{(r,s)}\right. \\
& \left. + \left(\frac{f_2}{f_2+3f_0} - \frac{1}{4}\right)m_{11}^{(r,s)}\right] \\
& \times \left[\left(\frac{1-f_2}{1-f_2+1-f_0} - \frac{1}{2}\right)m_{(21)}^{(r,s)}\right. \\
& \left. + \left(\frac{1-f_2}{1-f_2+3(1-f_0)} - \frac{1}{4}\right)m_{11}^{(r,s)}\right].
\end{aligned}
$$

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